APPROACHES TO THE DESIGN OF AGONIST AND ANTAGONIST PEPTIDE LIGANDS FOR NEUROPEPTIDE RECEPTORS AS PROBES OF BIOLOGICAL FUNCTION

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Intercellular communication is of central importance for the biological function of the central nervous system (CNS), and provides the means for a rapid response of the CNS to the environment and for the maintenance of homeostasis. The primary mechanism of intercellular communication involves the molecular interaction of a chemical messenger (e.g. a peptide neurotransmitter) with a receptor system (found in the plasma membrane). As a consequence of the neurotransmitter-receptor interaction a change in the properties of the cell occurs. A central issue is the chemical-physical basis for these changes. From this perspective the neuropeptide is a chemical bearing chemical information that is necessary to transform the receptor into its biologically active form.

Thus far it has been very difficult to obtain sufficient quantities of neuropeptide receptors in a biologically active form by either chemical isolation procedures or molecular biology. Furthermore, for many receptors, there appears to be two or more subtypes of these receptors, and the origins of, and reasons for, these subtypes are largely unknown. On the other hand, the structures of well over one hundred neuropeptides are known, and their biological properties often have been widely investigated including the development of in vitro and in vivo assay systems to assess their biological activities. However, these peptides often have severe deficiencies as ligands to examine the biological role(s) of the peptide. These include: 1) ready biodegradation; 2) lack of receptor selectivity; 3) high conformational flexibility; and 4) multiple biological effects. We and others have developed an approach to overcome these problems, and to design peptide ligands that can be used as tools to examine fundamental aspects of peptide-neurotransmitter interactions.

The approach involves the application of conformational and topographical constraint as part of the design. The basic hypothesis of this approach is that the three dimensional topography of the peptide and its dynamic properties are directly related to the information necessary for molecular recognition (binding) and transduction. Thus, in principle, both agonist and antagonist analogues can be developed utilizing this approach. Using this approach we have designed and developed peptides that are potent, highly receptor selective, and stable to biodegradation. Examples that illustrate the design principles and the biological insights that can result will be discussed. These will include the development of highly potent and receptor selective peptide ligands for the opioid receptors, and highly potent and prolonged acting analogues for the oxytocin receptor. As time permits other examples will be provided and the implications of these studies for future investigations will be discussed.

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